Chemoprevention of Cancers in Smokers and Ex-Smokers

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Goal

- Discover and develop chemopreventive agents effective against tobacco induced cancer, for use in smokers and ex-smokers

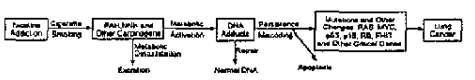
Chemotherapy and Chemoprevention

- Chemotherapy- treatment of cancer with toxic agents
- Chemoprevention - treatment of precancerous lesions or earlier changes with non-toxic agents

Rationale for chemoprevention of tobacco-*induced cancer*

- Prevention of smoking initiation and efficacy of smoking cessation have stalled since 1990
- There are 47 million smokers and 45 million ex-smokers in the U.S.- all at high risk for lung cancer and other tobacco-induced cancers
- There are 1.1 billion smokers worldwide
- Chemoprevention potentially can be coupled with smoking cessation

Scheme Linking Nicotine Addiction and Lung Cancer via Tobacco Smoke Carcinogens



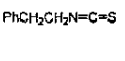
Molecular Targets

- Tobacco smoke carcinogens are targets for chemoprevention
- Targets for lung cancer prevention: BaP and NNK

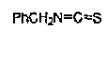
Rationale for Developing Isothiocyanates and Other Vegetable Constituents as Chemopreventive Agents for Lung Cancer

- Consistently, epidemiologic studies demonstrate that vegetable consumption is protective against lung cancer
- Hypothesis: there are cancer chemopreventive agents in vegetables
- Isothiocyanates and other vegetable constituents have good chemopreventive activity in animal models

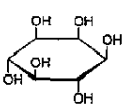
Structures of PEITC, BITC, and *myo*-inositol



PEITC



BITC



myo-inositol

Grid for Development of Chemopreventive Agents

	Rat	Mouse	Human
Efficacy			
Mechanism			
Toxicity			

Grid for Development of Chemopreventive Agents-PEITC

	Rat	Mouse	Human
Efficacy	NNK	NNK NNK + BaP	?
Mechanism	Inhibition of activation	Inhibition of activation-in part	Inhibition of P450s by watercress
Toxicity	13 week and 2 year studies-3 umol/g diet	3 umol/g diet is non-toxic	160 mg/day

Grid for Development of Chemopreventive Agents-BITC

	Rat	Mouse	Human
Efficacy	?	BaP	?
Mechanism	Induction of phase 2 enzymes	Inhibition of activation-in part	?
Toxicity	2.5 umol/g diet (25 weeks)	1 umol/g diet is non-toxic	14 mg/day

Grid for Development of Chemopreventive Agents- *myo*-Inositol

	Rat	Mouse	Human
Efficacy	?	BaP, NNK BaP + NNK Tobacco smoke	?
Mechanism	?	?	Reversal of BPDE induced inhibition of differentiation
Toxicity	15 mM in drinking water (47 weeks)	3% in diet	20 g/day

Limitations of Chemoprevention of Tobacco-Related Cancer

- Disincentive to cessation
- Low compliance
- Damage overwhelms agents
- Cost

Research Priorities: Chemoprevention

- Identify and develop effective agents
- Develop appropriate biomarkers
- Identify susceptible individuals
- Develop a pipeline for translation of preclinical data to clinical trials

Summary

- Chemoprevention is a potentially practical approach for reduction of cancer in smokers and ex-smokers.
- Tobacco smoke carcinogens are appropriate targets for chemoprevention.
- Mixtures of agents will be necessary for chemoprevention of tobacco-related cancer.
- Isothiocyanates and *myo*-inositol are appropriate constituents of this mixture based on efficacy, mechanism, toxicity